Project proposal with Chemical Biology Consortium Sweden

Instructions: Project proposals are uploaded directly as a **pdf file** into Anubis in the open call for larger CBCS project support. All material is considered confidential, and access is restricted to a limited group of CBCS Project Review Committee members and CBCS personnel under conditions of confidentiality, solely for the purpose of evaluating the proposed research.

The scope of the collaborative CBCS projects varies significantly and the different project types require different resources from CBCS. To ensure that we can deliver support to prioritized projects, we categorize the project proposals as below.

**(1) Assay Development project**

An example may include assay design, plate formatting, and assay optimization. This project type is applicable when:

* no suitable compounds are available for biological studies and an assay that meets the general screening requirements is not yet ready
* compounds are available but need optimization for biological/preclinical studies and an assay that meets the general optimization requirements is not yet ready

In conjunction with an assay development project, you can also apply for a screening campaign (project type 2) or chemistry activities (project type 5). If so, your project will seamlessly transition to type 2 or 5 without the need for an additional application, provided that the assay development project runs successfully according to a pre-agreed project plan between CBCS and the PI.

**(2) Screening project**

A typical example includes assay transfer efforts followed by the completion of a screening campaign, including hit confirmation and the first follow-up studies to characterize the value of identified hits. This activity can also include structure or ligand-based virtual screening campaigns. For studies further investigating the identified hits including the synthesis of hits and new analogs, or establishment of structure-activity relationship a new PRC proposal will be required. This project type is applicable when:

* no suitable compounds are available for the described biological studies and an assay that meets general screening requirements as listed in the technical feasibility section is available
* a crystal structure of the target protein exists and there are no suitable compounds for the described biological studies
* no suitable compounds are available for the described biological studies but ligands for the protein target are known

If the general screening requirements are not met, you should also apply for an assay development project (project type 1).

**(3) Target identification/mode of action project**

This type of project typically follows a phenotypic screening campaign, and the main goal is to understand the molecular targets or mode of action of a compound or hit series. Techniques used for these projects are often multidisciplinary and can include Cell Painting, CRISPR screening, and proteomics-based approaches. This type of project is applicable when:

* a hit compound has been sufficiently validated, e.g. demonstrates efficacy in dose-response studies, and is not ruled out in counter screens or validation screens
* the compound is sufficiently cell penetrable for downstream studies
* in the ideal scenario an inactive close analogue of the hit compound has been identified

In some cases, it may be desirable to establish a structure-activity relationship for the compounds series before the identification of the target/MOA. In such situations choose an Enabling Chemistry (type 5 project) as well.

**(4) Compound or disease profiling project**

This type of project includes the profiling of disease models against libraries of compounds in functional precision medicine studies, as well as Cell Painting studies. This type of project is applicable when:

* Characterized disease models exist
* Relevant compound libraries exist

If the general optimization/SAR requirements are not met, you should also apply for an assay development project (project type 1).

**(5) Enabling chemistry project**

A typical example includes optimization activities post a screening campaign or otherwise identified small molecule modulators. More specifically, the request to optimize or modify compounds to suit the needs of the investigator may require activities such as structure-activity relationship (SAR) studies, *in silico* and/or *in vitro* physicochemical or pharmacokinetic characterization, and the various *in vitro* pharmaceutical profiling tests available. This can also include in silico hit expansion and lead optimization through rational drug design or virtual screenings. This project type is applicable when:

* no suitable compounds are available for the described biological or preclinical studies but there is a chemical starting point, a confirmed hit compound with dose-response activity, that needs further optimization and/or SAR investigation.
* an assay that meets the general optimization/SAR requirements as listed in the technical feasibility section is available
* if desired, data for in silico hit expansion can be delivered

If the general optimization/SAR requirements are not met, you should also apply for an assay development project (project type 1).

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| --- | --- |
| Date of Submission | Click here to enter a date. |
| Principal Investigator |       |
| Primary Affiliation |        |
| Application for project type (1-5) |       |

Title of proposal

Abstract (max 750 characters)

Background and expected scientific impact (please be as concise as possible, max 3 pages)

(1) What scientific need does the proposed project address and what is the broader impact of the proposed study? Please explain what makes your proposed approach unique. Include any relevant literature references, figures, and tables.

Click here to enter text.

(2) Are small molecule tools already available for the current purpose? Please clarify why existing compounds, when available, cannot be used for this research purpose. If no small molecule tools exist are there other therapeutic modalities (e.g. antibodies, PROTACs, etc) that modulate the same biology? Ensure you have made a detailed search or contact CBCS for assistance. Include relevant literature references. (Note: This section may not be relevant for functional precision medicine and Cell Painting projects).

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(3) Are there disease models in place for functional precision medicine studies or Cell Painting projects? Please describe their disease relevance and characterization.

Click here to enter text.

(4) Does your project require an ethical permit, an addendum to the existing ethical permit, or a material transfer agreement?

Click here to enter text.

Project goals and publication strategy (max 1 page

(5) What are the short and long-term goals of the proposed project?

Click here to enter text.

(6) Chemical biology projects are complex and often require significant validation steps including validation in multiple model systems and detailed mechanism of action studies. Please detail the steps to gather this information for your project to ensure the identification of a robust small-molecule tool. This includes relevant validation and follow-up studies that align with the envisioned publication strategy and potential intellectual property interests, if applicable. Suggest a tentative journal for publication for a successful project and explain which aspects require input/resources from CBCS. Please comment on the importance of CBCS efforts in project completion. This planwill often determine the requirements for validation of tool compounds, eg if animal models are necessary. Illustrations to describe the project flow and key decision points may be beneficial.

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**Technical description and feasibility (max 3 pages)**

Most chemical biology projects are based on an assay (a primary screening assay, a SAR driving assay, or an otherwise needed method) used to initially assess the value of small molecules. Information on the the current status of this assay and planned follow-up activities for the project is essential to estimate the resources required to carry out and publish the proposed work. For chemistry proposals including SAR studies, the assay must have a dynamic range, *i.e.* is sensitive enough, to rank small molecules with potencies of different orders of magnitude.

**Questions for project types 1-4.**

*Assay Development, Screening, Target ID/MoA, or Compound/disease profiling projects.*

(7) Give a detailed technical description of the assay and outline the successive steps. Describe the format of the assay (96- or 384-well plate format or another non-plate-based format). Include information on available positive and negative controls and describe their biological relevance.

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(8) Please described the approximate size of the compound library/libraries to screen? Is a diversity set of interest or known tools or drugs? If unsure on available compound libraries please resach out to CBCS staff scientists.

Click here to enter text.

(9) List the availability of reagents and cells, their source (in-house production or commercial), and estimated costs of the reagents needed to perform a screening campaign of the number of compounds stated in *question (10).* If cell lines/reagents are not yet in place, give an estimate of the date when they will be ready to use.

Click here to enter text.

(10) Show all current experimental data illustrating the performance of the assay: relevant controls, Z’ factor (for a screen project Z’>0.5 is desirable), signal to background ratio, DMSO tolerance, reagent stability, and plate edge effects.[[1]](#footnote-1) If your assay is at a stage where this is not applicable please explain what steps are lacking. For functional precision medicine assays characterization of disease relevance or plans for these studies are necessary.

Click here to enter text.

(11) Describe the availability and current status (up and running/under construction/at the planning stage) of an appropriate counter assay[[2]](#footnote-2) and an assay with an orthogonal readout

Click here to enter text.

(12) List the secondary assays or model systems required to achieve the project goals and intended publication strategy. These assays may include biophysical, biochemical, cellular assays, and (if applicable to your project) in vivo models. If specificity or selectivity for a particular biology is necessary, provide details on the assays to assess this. Indicate the current status of all secondary assays, specifying whether they are up and running, under construction, or at the planning stage. For assays not presently available in your lab, outline the plans for accessing them, either through other research infrastructures or alternative means.

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(13) If in silico studies like virtual screening are planned describe steps and available data (e.g. crystal structure).

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**Questions for project type 5**

*Enabling chemistry (must include a description of the SAR-driven assay)*

(14) Describe the chemical series including identification, validation studies, and intended sites for modification. Pre-existing data (target structure and/or existing preliminary SAR) can be used to generate rational hypoteses using structure- or ligands-based approaches.

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(15) Give a detailed technical description of the intended SAR driving assay or alternative method for compound testing. Outline the steps, and describe the assay format. Include information on available controls/reference compounds and describe their biological relevance.

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(16) Present experimental data with the intended reference compound demonstrating a dose-response experiment (n=3 with a minimum of 7 points) tested at a minimum of two independent occasions. Have several compounds with different potencies been tested in the SAR driving assay?

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(17) If in silico studies are planned describe steps and available data (eg crystal structure). Pre-existing data (target structure and/or existing preliminary SAR) can be used to generate rational hypoteses using structure- or ligands-based approaches.

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(18) Suggest secondary assays such as selectivity assays, cellular assays, and *in vivo* models (if applicable to your project) and describe the current status (up and running/under construction/at the planning stage). For assays not available in your lab, please describe plans for accessing them (via other research infrastructures or else).

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(19) Describe any available plans (if applicable) for pharmaceutical property profiling (ADME properties)?

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**Detailed project plan (max 2 pages)**

(20) Please consult CBCS personnel to provide information on the proposed research project plan by listing activities and potential milestones in the table below (Table 1). These activities should align with your overall project and publication plan described aboveFor each activity, explain the tentative time required, which aspects of the project require input/resources from CBCS, and the current availability of different types of resources (human, financial, and instrumentation). All technical/scientific details relating to each activity and milestone should be provided in the section on technical feasibility (see above).

**Table 1. Summary of all project activities to reach publication**

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| --- | --- | --- | --- |
| Project activity*E.g.,* assay development, assay transfer, assay optimization, assay validation, screening, hit confirmation, enabling chemistry, efficacy models, in vivo studies, *etc.* | Time (months)a | Responsibleb | Resourcesc |
| **Human***(e.g.,* postdoc or Ph.D. student) | **Financial**(Secured or unsecured) | **Instrument**(Available in-house, yes or no) |
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| (a) Estimated time for a full-time employee to complete these activities; (b) Indicate who will be primarily responsible for resourcing the activity (CBCS, PI, co-PI, CRO, etc.); (c) Please specify PI resources as human: *e.g.* postdoc or Ph.D. student/financial: secured or unsecured/instrument: available in-house yes or no. |

(21) Propose at least one stop/go decision point relating to any uncertainties concerning the technical feasibility as described above.

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(22) Have you contacted CBCS personnel and discussed the proposal and project plan in detail (required for submission)? Specify CBCS node and person.

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# Additional Comments

(Please enter any additional comments you see fit to clarify your proposal)

1. If you are not familiar with these terms, please see e.g. the Assay guidelines manual [Internet], available from: https://www.ncbi.nlm.nih.gov/books/NBK53196/ (Sittampalam GS, Coussens NP, Brimacombe K, et al., editors. Bethesda (MD): Eli Lilly & Company and the National Center for Advancing Translational Sciences; 2004-), or contact CBCS personnel for assistance. [↑](#footnote-ref-1)
2. The purpose of a counter assay is to identify compounds that interfere with the read-out in the primary assay by *e.g.* auto-fluorescence. A counter assay can also be used to identify compounds with undesirable properties such as cytotoxicity. [↑](#footnote-ref-2)